N19123

APPROV.
LETTER

NDA 19-123

Upsher-Smith Laboratories, Inc.
Attention: Mr. Fred J. Wehling
14905 23rd Avenue North
Minneapolis, MN 55441

Dear Mr. Wehling:

Please refer to your new drug application dated September 16, 1985 resubmitted on April 5, 1985 under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Klor-Con (potassium chloride) 8 and 10 mEq Slow Release Tablets.

We also acknowledge receipt of your amendment dated November 27, 1985.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved. Prior to marketing, however, please submit twelve copies of the final printed labeling that are identical to the draft. Please individually mount seven of the copies on heavy weight paper or similar material.

In the near future, we plan to request revision of current potassium chloride labeling that incorporates endoscopy study findings as well as content and format specifications. We do expect your cooperation in making changes after our internal deliberations have been completed.

Marketing of the drug before the final printed labeling is submitted to FDA renders the product misbranded under 21 U.S.C. 352.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

In addition, please submit, in duplicate, the advertising copy that you intend to use in your proposed introductory promotional and advertising campaign. Please submit one copy to this division and the second, along with a copy of the package insert directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 16B-64
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

Be reminded that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.50 and 314.51.

If you have any questions, please contact:

Mr. Peter Pavilla
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc: Ellis Pharmaceutical Consulting, Inc.
Attention: Ms. Nanni Levi Ellis
912 State Road
Princeton, NJ 08540-1414

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-240 (with labeling)
HFN-83
HFN-232 (with labeling)
HFN-110/Pavilla/12/18/85
pam/12/18/85/2562e
R/D init: Rosenthal/12/20/85
Walters/12/20/85
Chesnick/12/20/85
Gleason for Chesnick/12/24/85
Wargenstern/12/24/85

APPROVAL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
DIVISION DIRECTOR'S REVIEW

NDA: 19-123

Sponsor: Upsher-Smith Laboratories, Inc.
14905 23rd Avenue North
Minneapolis, MN 55441

Product: Trade Name, Klor-Con (8 and 10 mEq dosage forms)
Generic Name, Sustained release, wax-matrix, oral, solid dosage form of KCl

Date of Submission: August 16, 1983, resubmitted August 16, 1984, non-approvable letter issued December 1984, resubmitted.

Date of Review: April 15, 1986

After some time, this NDA is now approvable. The major problem related to previous non-approvability was the bioavailability study originally submitted by Upsher-Smith. The data have been re-analyzed and submitted on November 27, 1985. This submission and its data make the necessity of consulting our biostatisticians (which was thought to be necessary at our meeting with Upsher-Smith on November 6, 1985) unnecessary and the problems discussed in the entire meeting of November 6, 1985 are essentially moot.

As it now stands, there is no statement by the Division of Biopharmaceutics that the Upsher-Smith bioavailability study is acceptable. I have not referred the November 6, 1985 submission to the Division of Biopharmaceutics and this review constitutes my own review of that study which I find adequate, based on the November 6, 1985 analysis.

Prior to reviewing the study, a brief statement of my review regarding the purposes of a bioavailability study for a KCl product is in order.

At present, no one has devised a better method for assessing bioavailability than to administer the KCl product orally and to concomitantly measure the appearance of K ion in the urine. Orally administered potassium enters a large body pool when and if absorbed and the K which comes out in the urine may or may not represent any of the actual K administered orally. At the limit, all of the K administered orally could be absorbed but none come out in the urine.

Consequently, even though studies try to establish steady-state with respect to intake of dietary potassium and try to ensure adequate urine volume so that

The mean 24-hour cumulative excretion of potassium is not statistically, significantly different between any of the treatment. The sponsors do not have a power calculation, and I did not perform one, so I cannot say what confidence one can have that if there had been a difference one could have, detected the difference.

However, the preamble to this review asserts that bioequivalence is not required of oral, solid, dosage forms of KCl. One cannot determine rate and extent of absorption from experiments of this type, so an absolute bioequivalence statement cannot be achieved; even if sufficient power is present to directly compare any measurements made. The various KCl formulations are not generically equivalent and are not (in fact should not) be dispensed interchangeably. So not being able to make a firm statement with respect to "extent," in its loosest sense, is no detriment with respect to decisions regarding approvability.

My conclusion then is that the Klor-Con tablets are bioavailable and from that vantage point meet that standard for approvability. The studies were reasonably designed, poorly conducted and reluctantly analyzed, but the result, with respect to bioavailability, is sufficient to form a basis for approval.

The time course of potassium excretion is shown in Figure 1. The visually apparent difference between Klor-Con-10% and all sustained release formulations (between 0 and 6 hours) was statistically significant at a p value of 0.0027. This reasonably establishes that the Klor-Con tablets exhibit sustained release properties *in vivo* and consequently can be labelled as a sustained release formulation.

Summary

I see no outstanding issues that need resolution. The edited package insert is reasonable. It is to be updated sometime soon and the approval letter should so indicate. This memo and the appended disclosable reviews constitute the SBA.

Ray Lipicky

Raymond J. Lipicky, M.D.
Division Director

cc:
[redacted]
HFN-110
HFN-110/CSO
HFN-110/RLipicky
ef/4/28/86/00500g

bad feature of the study. All 24 subjects completed the study and values for all 24 subjects were used for all calculations.

The study lasted a total of 19 days during which a planned diet consisting of about 50 mEq potassium and 3000 ml of liquid (not enough) were ingested per day. A 4-day lead in period was planned (the 5th day being the first dosing day) and dosing occurred every 5th day thereafter. Fractionated urine collections obtained on the 4th day were used to correct for baseline potassium excretion. If the baseline urinary potassium, at any interval, was greater than that on a dosing day (which would have been a negative value when subtracted) the value for the difference was set to 0.

There were 768 estimates of urinary potassium, 197 values of 0 were assigned to the baseline substracted values, essentially about a 25% incidence of indeterminate values. Two subjects for two treatment periods each had 0 values assigned for all collections and one subject had 0 values assigned for one treatment for all collections. Seventy-three (almost 40%) of missing values were for the first 2 (0-1 hour and 1-2 hour) collections, the reminder were scattered between the 3rd (2-3 hour) and 7th samples (8-12 hour) with only 5 out of 96 values being 0 in the last collection interval (12-24 hour).

The baseline corrected mean (± SEM) cumulative urinary excretion of potassium, 0 to 24 hours is given in the following table.

Figure 1

Drug	Mean 0-24 hour potassium excretion	SEM
Klor-Con 8 mEq	21.71 mEq	2.06
Klor-Con 10 mEq	24.82 mEq	2.15
Slow-K	21.87 mEq	2.08
Klor-10%	23.05 mEq	2.0?

The probabilities that the mean baseline subtracted, cumulative 24-hour potassium excretion was 0 were 0.0001, 0.0001, 0.0001 for Klor-Con 8 mEq, Klor-Con 10 mEq, Slow-K and Klor-10%, respectively. Consequently, one can conclude with reasonable certainty that some potassium was absorbed from each of the potassium formulations and consequently Klor-Con 8 mEq and Klor-Con 10 mEq are bioavailable.

The potential error of assuming 0 values, when the baseline was greater than on drug day (i.e., would have yielded a negative value) are inconsequential to the major conclusion. Not only does K come out of the wax matrix when the tablet is placed in water in a rotating bottle, it also does so in vivo.

urine collections can be made at short intervals (to measure rates of excretion as best as possible), under the best of conditions a KCl bioavailability study cannot measure the rate and extent of absorption. These are the two estimates one desires of a bioavailability study and are the two parameters that judgments with respect to bioequivalence are made from; a comparison of area under the curve is generally not suitable for a bioequivalence determination.

So then, what can one conclude from a bioavailability study of orally administered KCl? The answers seem straight forward enough.

1) One can conclude that some of the administered dose is absorbed even though one cannot explicitly conclude how much of the administered dose was absorbed. By comparing the urinary excretion between several formulations, including a solution of KCl, one can hope to make some crude relative comparisons but a bioequivalence statement cannot be made.

2) By comparing the time of peak urinary excretion rates (at mid-collection point) occurring after each formulation tested to the time of peak urinary excretion rates, occurring after KCl in solution, one can determine that the formulation in vivo has slow release characteristics. This deduction has unverifiable assumptions and even if in vivo slow release is not documented, the only consequence is that one could not make a slow release claim.

With respect to rates of excretion, if one cannot obtain voided samples of urine at close enough intervals, the estimate of rate will be poor. That is, if the rate estimates were based upon a single 24-hour collection interval and similar amounts were excreted over that interval, all rate estimates would be identical even though enormous differences in rates may have been present early in the 24-hour period.

With respect to the Upsher-Smith study, it is known (from an on-site inspection as well as from evaluation of the data) that care was not taken to adequately hydrate the subjects and there were missing values for urinary concentrations of K for many subjects, especially at early collections (0 to 1-hour samples because the subjects were not able to void at the commanded times). In general, the study did not seem well run, however, I believe conclusions can be drawn and the data support approval.

The Study

Twenty-four normal, male volunteers were involved in four way, planned sequence, cross-over trial. Each of the four treatments involved oral administration of 40 mEq KCl (tablets of the 8 mEq Klor-Con, 4 tablets of the 10 mEq Klor-Con, 5 tablets of Slow-K and 30 ml of a 10% solution of KCl as Upsher-Smith's Klor-10%), which is a relatively low dose and is an additional

LBLING

KLOR-CON®

[redacted] Chloride
[redacted]-release
[redacted] U.S.P.
[redacted] and 10 mEq

DESCRIPTION

KLOR-CON® Extended-release tablets are film coated (not enteric-coated) tablets containing 600 mg (equivalent to 8 mEq) or 750 mg (equivalent to 10 mEq) potassium chloride in an inert matrix. Potassium chloride has an empirical formula of KCl and its molecular weight is 74.55. This oral potassium supplement formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract. The expended matrix is not absorbed and may be excreted intact in the stool.

Inactive Ingredients: Castor oil, D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), hydroxypropyl methylcellulose 2910, magnesium stearate, polyethylene glycol 3350, propylene glycol, synthetic iron oxide, and other ingredients.

CLINICAL PHARMACOLOGY

Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle and the maintenance of normal renal function.

Potassium depletion may occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of prolonged therapy with oral diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, severe diarrhea, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Potassium depletion due to these causes is usually accompanied by a concomitant deficiency of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases flaccid paralysis and/or impaired ability to concentrate urine.

Potassium depletion associated with metabolic alkalosis is managed by correcting the fundamental causes of the deficiency whenever possible and administering supplemental potassium chloride, in the form of high potassium food or potassium chloride solution or tablets.

In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hypercalciuria. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, or potassium acetate.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH EXTENDED-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

[redacted] hypokalemic are in patients with hypokalemia with or without metabolic alkalosis, or digitalis intoxication [redacted] with hypokalemia-induced paralytic paralysis.

2. Prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain carbonic anhydrase states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have adequate dietary potassium. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene, or amiloride).

Non-enteric potassium chloride preparations have produced esophageal ulceration in cardiac patients with esophageal compression due to an enlarged left atrium.

All solid-dosage forms of potassium supplements are contraindicated in any patients in whom there is clinical [redacted] or delay in tablet passage through the gastrointestinal tract, as in these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

Antagonism with Potassium-Sparing Diuretics: Hyperkalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene, or amiloride), since the simultaneous administration of these agents can produce severe hyperkalemia.

[redacted]

Each tablet contains: potassium chloride — 600 mg.

Usual Dose: Consult package insert — dose should be individualized.

Dispense in a tight container as defined in the U.S.P. with a child-resistant closure.

Store at controlled room temperature 59°-86°F (15°-30°C).

Protect from light and moisture.

NDC 0245-0040-11
100 Tablets

KLOR-CON® 8

Potassium Chloride
Extended-release
Tablets, U.S.P.
8 mEq (600 mg)

CAUTION: Federal law prohibits dispensing without prescription.

Rev. 0000 42-0011

Manufactured by
UPSHER-SMITH
LABORATORIES, INC.
Minneapolis, Minnesota

Each tablet contains: potassium chloride — 750 mg.

Usual Dose: Consult package insert — dose should be individualized.

Dispense in a tight container as defined in the U.S.P. with a child-resistant closure.

Store at controlled room temperature 59°-86°F (15°-30°C).

Protect from light and moisture.

NDC 0245-0041-11
100 Tablets

KLOR-CON® 10

Potassium Chloride
Extended-release
Tablets, U.S.P.
10 mEq (750 mg)

CAUTION: Federal law prohibits dispensing without prescription.

Rev. 0000 42-0011

Manufactured by
UPSHER-SMITH
LABORATORIES, INC.
Minneapolis, Minnesota

NDC 0245-0040-15
500 Tablets

KLOR-CON® 8

Potassium Chloride
Extended-release tablets, U.S.P.

8 mEq (600 mg)

Each tablet contains: potassium chloride — 600 mg.

Usual Dose: Consult package insert — dose should be individualized.

Dispense in a tight container as defined in the U.S.P. with a child-resistant closure.

Store at controlled room temperature 59°-86°F (15°-30° C). Protect from light and moisture.

CAUTION: Federal law prohibits dispensing without prescription.

Rev. 0000 42-0040

UPSHER-SMITH

500 tablets

Manufactured by
UPSHER-SMITH
LABORATORIES, INC.
Minneapolis, Minnesota

NDC 0245-0041-15
500 Tablets

KLOR-CON® 10

Potassium Chloride
Extended-release tablets, U.S.P.

10 mEq (750 mg)

Each tablet contains: potassium chloride — 750 mg.

Usual Dose: Consult package insert — dose should be individualized.

Dispense in a tight container as defined in the U.S.P. with a child-resistant closure.

Store at controlled room temperature 59°-86°F (15°-30° C). Protect from light and moisture.

CAUTION: Federal law prohibits dispensing without prescription.

Rev. 0000 42-0041

UPSHER-SMITH

500 tablets

Manufactured by
UPSHER-SMITH
LABORATORIES, INC.
Minneapolis, Minnesota

MED REVIEW

1.1

JUL 20 1984

Division of Cardio-Renal Drug Products
Medical Officer's Review

NDA: 19-123 Review Date: July 5, 1984

Sponsor: Upsher - Smith Laboratories, Inc.
14905 23rd Avenue North
Minneapolis, MN 55441

1. General Information

(a) Drug Name: Klor-Con (potassium chloride in 8 mEq and 10 mEq film coated, wax matrix, controlled release oral tablets)

(b) Proposed Indications: The customary indications for oral potassium supplements, including the treatment of hypokalemia, digitalis intoxication and hypokalemic periodic paralysis, and the prevention of hypokalemia in selected patients.

2. Manufacturing Controls

Refer to Chemistry Review.

3. Pharmacology

A. Pharmacokinetics

The sponsor has submitted one human bioavailability study (Vol. 1.2, p 10.0000). This is a four way, planned sequence, cross-over trial in 24 normal male subjects, comparing the bioavailability of 40 mEq doses of Klor-Con 8 mEq, Klor-Con 10 mEq, Slow-K, and 10% KCl solution. Subjects were confined and maintained on a diet containing 50 mEq potassium and 3,000 ml of liquid per day. Bioavailability was assessed by urinary potassium excretion over the 72 hours after administration of each of the four test drugs. The sponsor has reported and analyzed data for mean urinary K excretion for each test drug with respect to the entire 72 hour period and various fractions thereof. Adjustments were made for the contribution of dietary potassium to potassium excretion. After these adjustments, there were no significant differences between any of the four preparations during any of the intervals up to 72 hours. For more detailed information, refer to the Biopharmaceutics review.

B. Toxicology

The sponsor submitted one study of animal toxicology in cynomolgus monkeys. Four parallel groups of monkeys, each containing three males and three females, received Klor-Con 10 mEq, Lilly Enseals, Slow-K, or empty gelatin capsules. KCl was administered at a dose of 3000 mg. The results of this study are presented in the table below, taken from the Pharmacology review. They show large bowel lesions in the Enseals group only, and an acceptable level of small bowel and gastric toxicity for Klor-Con. The study is acceptable. For more detailed information, refer to the Pharmacology review.

Table I
Results of Monkey GI Irritation Study

Form, Tabs	Dosage, mEq	Tabs mg	Dosage/Day	Diarrhea + soft stools	LESIONS Stomach	S-I	L-I
Control	2	2			0/6	0/6	0/6
Lilly Enseals 13m Eq	2	1	3000 mg 508 to 1000 mg/kg	2/4	1/6 h 1/6 U	1/6 h (882mg/kg)	1/6 U 1/6 e
Slow-K 8m Eq	3	2	3000 mg 508 to 1000 mg/kg	4/4	1/6 h 3/6 U		
Klor Con 10m Eq	2	2	3000 mg 508 to 1000 mg/kg	2/4	1/6 U (M 769 mg/kg)	1/6 h (ileocecal valve).	

U = ulceration; e = erosion; h = hemorrhage

4. Clinical Studies

The sponsor submitted the results of two clinical studies, a multicenter use trial and a comparative upper GI toxicity trial.

1. The Use Trial (Vol.1.2-1.4)

Two investigators were involved in this trial. One was Jack Blackshear, M.D. of Little Rock, Arkansas, and Jules Kann, M.D. of Pittsburg, PA. Each investigator used the same protocol, but the results were presented separately.

The design of the trial was simple and straightforward. The study population consisted of hypertensive adults receiving antihypertensive therapy and potassium supplementation at any dose up to 80 mEq/day. No exclusion criteria were listed. Before starting study drug, each patient had a CBC, a UA, a standard automated chemistry panel, a stool for occult blood, and an ECG. Patients were then openly switched from their prior potassium replacement (Slow-K in most cases) to an approximately equivalent dose of Klor-Con 10 mEq, given in two divided doses. Serum potassium and stool for occult blood were checked at 2, 4 and 8 weeks (the end of the study). Patients were interrogated concerning adverse reactions at each of the three repeat visits. Patients also had a physical exam at the end of the study.

Forty patients enrolled in Dr. Blackshear's arm of the study. Each patient had been taking three 8 mEq Slow-K tablets. All of these patients were started on Klor-Con at a dose of 20 mEq/day. Twenty-two patients remained on this dose throughout the entire eight week trial, while 12 had their dose increased to 30 mEq/day, and another six had an increase to 40 mEq/day.

No patient reported any side effects, and all of the 160 stools for occult blood in this study were negative.

The mean serum potassium level for the 40 patients in this study rose from 3.7 mEq/liter at baseline (range, 2.7 to 4.8 mEq/L) to 3.9 mEq/liter at eight weeks (range, 2.8 to 4.9 mEq/L). At baseline, 14 patients had serum potassium levels below 3.5 mEq/liter, compared to four patients at day 56.

In Dr. Kann's arm of the study, there were 22 patients. These patients were somewhat more variable in their prestudy potassium dosage, which ranged from 4 to 60 mEq/day. When patients were switched to Klor-Con, the dose they were given was in most cases slightly higher than the dose prior to the trial, in contrast to Dr. Blackshear's study, in which the opposite was true.

No patient in Dr. Kann's study had any adverse reactions. However, while all of the patients had negative stools for occult blood at baseline, three of the 22 patients had one subsequent trace positive stool for occult blood, while one other patient had two subsequent trace positive stools for occult blood. None of these patients had any symptoms.

Relevant data for those four patients is presented in Table 2 below:

Table 2
Patients with Positive Stools

Pt Age	Sex	KCl Dose in mEq/day	# of Pos. Stools	Baseline Hct	Final Hct
59	F	20	2	46.0	43.9
56	F	20	?	42.3	40.8
56	F	20	1	46.1	45.0
43	F	30	1	44.2	44.5

Hct = hematocrit

In this arm of the study, serum potassiums at baseline ranged from 3.1 to 5.7 mEq/liter, with a mean of 3.5. At the end of the study, they ranged from 3.1 to 5.6, with a mean of 3.87. Serum potassium levels less than 3.5 mEq/liter were present in 13 out of 22 patients at baseline but only in 3 of 22 patients at the end of the study.

Reviewer's Note: This appears to be an adequate use study both in terms of the limited amount of safety data and efficacy data presented.

2. Upper GI Toxicity Study (Vol. 2.1)

The investigator for this trial was Kenneth Krantz, M.D., Ph.D., of Kansas City, Missouri.

This was a randomized, three-way, parallel-group study in subjects confined over 11 days. The study was open label, but blindly evaluated.

Subjects were healthy adult males between the ages of 18 and 45 with normal CBC, urinalysis, stool for occult blood, EKG and routine blood chemistry. All subjects had normal physical exams and no history of GI disease. In addition, all subjects were required to have normal U.I mucosa on a screening endoscopy performed immediately prior to entry into the study. It is not clear how many patients were screened in order to provide the 30 study subjects.

Subjects were confined and placed on a hospital diet with no red meat, turnips, or horseradish. High fiber foods were included to provide bulk to facilitate stool collection for daily stools for occult blood.

On the day after the screening endoscopy, all study subjects were begun on glycopyrrolate 2 mg tid. In addition, patients were randomly allocated to receive Klor-Con 10 mEq tablets (70 mEq daily), Slow-K 8 mEq tablets (72 mEq daily), or placebo tablets (6 tablets daily). Study medications were taken three times daily after meals for 7 days. No concomitant medications were allowed.

On the day after study medications were discontinued, patients were re-endoscoped. All endoscopies in this study were performed blindly by a single endoscopist. The following scoring system was used: 0 = no lesions; 1 = one mucosal hemorrhage; 2 = more than one mucosal hemorrhage. Scores as high as 6 were to be given for more severe lesions, but no subject received a lesion score greater than 2. Erythema was noted, but not assigned on a numerical value. The esophagus, stomach, and duodenum were each graded, and their scores were reported.

The three study groups were comparable in terms of age, weight, and vital signs. All patients completed the study. The initial endoscopy for all patients was normal.

The results of the final endscopy are summarized in Table 3. No patient had gradeable lesions in more than one anatomic region, and only the most severe lesion score is reported for any patient.

Table 3
Endoscopy Study Results

Drug	Fraction with Lesions	# with Erythema	# with Grade 1	# with Grade 2
Klor-Con	4/10	3	1	0
Slow-K	1/10	0	1	0
Placebo	7/10	1	4	2

The sponsor stated that none of the lesions were believed to be clinically significant, and all could be considered as chance events in normal subjects.

There were no positive stools for occult blood in the study.

In the ten patients taking Klor-Con, four complained of abdominal pain or vomiting at some time during the period of drug administration. In the Slow-K group, these symptoms were reported by three patients. In the placebo group, four patients reported one or more of these symptoms. In no patient were these symptoms considered serious.

Reviewer's Note: The study is acceptable. The lack of serious lesions in persons receiving Klor-Con and Slow-K is consistent with limited data from other gastroscopy studies suggesting that administration of wax matrix products with or after meals is associated with a comparatively low incidence of UGI erosions and ulcers. The finding of grade 2 lesions in two placebo subjects suggests that the (blinded) endoscopist did not systematically grossly under-read the endoscopic evaluations. These results, together with the findings of the monkey study and the use trial, suggest that the UGI irritant potential of Klor-Con is acceptable.

5. Labeling Review

The proposed labeling for Klor-Con is generally consistent with the labeling for Slow-K and other solid dose KCl products.

However, the paragraph on bioavailability (found on page 04 - 0021 of Vol 1.1) is somewhat ambiguous, and should be reworded. The second sentence of that paragraph should read "there were no significant differences in the cumulative amount of potassium excreted over periods of 24, 48, or 72 hours between 40 mEq doses of Klor-Con 8 mEq, Klor-Con 10 mEq, 10% potassium chloride solution, and a reference 8 mEq slow release tablet."

6. Conclusion and Recommendations

The NDA is approvable. A minor change in labeling is discussed under the previous heading.

Martin Rose, M.D.

CHEM REVIEW

Division of Cardio-Renal Drug Products
CHEMIST REVIEW NUMBER TWO

Completed: November 28, 1984
(Twenty days since last amendment)

A. 1. NDA 19-123 ORIGINAL NEW DRUG APPLICATON-AS AMENDED

Applicant: Ellis Pharmaceutical Consulting, Inc.
913 State Road
Princeton, New Jersey 08540-1484
Telephone: (609) 924-7212
for

Upsher- Smith Laboratories, Inc.
14904 23rd Avenue North
Minneapolis, MN 55441
Telephone: (612) 472-4412
Fred J. Wehling
Director of Regulatory Affairs

2. PRODUCT NAMES:

Proprietary: KLOR-CON 10 mEq (750 mg) (Potassium Chloride) Slow Release Tablets

KLOR-CON 8 mEq (600 mg) (Potassium Chloride) Slow Release Tablets

Non-proprietary: Potassium Chloride 750 mg per tablet
Potassium Chloride 600 mg per tablet

USAN: Potassium Chloride

Compendium: USP XX (1980), Page 642, and 5th Supplement page 1065. [N.B. USP XXI is not yet offical].

3. DOSAGE FORM: Extended-release tablet. Oral route. Rx N.B. These tablets are not enteric coated but they are film coated to control the release of potassium ion from the matrix.

4. PHARMACOLOGICAL CATEGORY: Hypertension in adults requiring controlled release potassium supplement in order to maintain normal serum K^+ level.

PHARM
REVIEW

Review and Evaluation of Pharmacology and Toxicology Data
Original Summary

Category: Slow-release potassium chloride preparation for potassium supplementation

Composition: film-coated tablet containing 600 mg (8mEq) or 750 mg (10 mEq) of potassium chloride in an inert, non-absorbable matrix

Indication: for therapeutic use in patients with hypokalemia with or without metabolic alkalosis and for prevention of potassium depletion; usual dosage is in the range of 20 mEq (1500 mg) per day for hypokalemia and 40-100 mEq (3000 - 7500 mg) per day for treatment of potassium depletion

Related IND: [redacted]

Related NDA: 17-476; Slow-K (Ciba-Geigy)

Summary and Evaluation

Sponsor has submitted an NDA for a slow-release potassium chloride product similar pharmacokinetically to the wax matrix products such as Slow-K, but with a non-eroding polymeric film coating which controls the release of the potassium rather than a sugar-coated slowly dissolving wax matrix formulation. A gastrointestinal toxicity study of Klor-Con was conducted in Cynomolgus monkeys for 5 days. This study was previously reported under IND 19,251 and evaluated by Pharmacology Review dated 8/11/82. In this study, Klor-Con was compared to Slow-K and an enteric-coated product (Enseals). The dose for each was 3000 mg/day (600-1000 mg/kg) given in 2 divided doses. A control group was also included. The results for GI toxicity can be seen below:

Table of Microscopic Pathology

	Stomach	Small Intestine	Large Intestine
Control	0/6	0/6	0/6
Enseals	1/6-H 1/6-U	1/6-H	1/6-U 1/6-E
Slow-K	1/6-H 3/6-U		
Klor-Con	1/6-U	1/6-H	

As can be seen from these results, Klor-Con caused less drug-related GI toxicity than the comparative slow-release product, Slow-K, and no small or large bowel ulcers. The enteric-coated tablet did not produce the typical small bowel lesions usually seen with this product, although large intestinal lesions were observed. The reason for this may be that Enseals behaves more like a slow-release product, pharmacokinetically.

Recommendation

This NDA would be recommended for approval.

James P. Burns, Jr., Ph.D.
3/28/84

cc: Orig.
HFN-110
HFN-110/CSO
HFN-110/JPBurns
sn/3/29/84/5601c

BIO
REVIEW

Shah
NOV 6 1985

Potassium Cl
Klor-Con^{R} SR
600 mg tablets
750 mg tablets
NDA # 19-123
Reviewer: Irma Benedek
[redacted]

Upsher-Smith Labs.
Minneapolis, MN
Submission Date:
July 31, 1985

Review of a Bioequivalence Study

This submission has been reviewed by the Division of Biopharmaceutics and the study was rejected. The Division of Bioequivalence recommends that the firm conduct a new bioequivalence study. Therefore, no further action is needed at this time.

Irma Benedek, Ph.D.

Irma Benedek, Ph.D.
Division of Bioequivalence
Review Branch 3

RD INITIALED RMhatre
FT INITIALED RMhatre Ramakant M. Mhatre 11/5/85

IBenedek[redacted]10/29/85[redacted]

cc: NDA # 19-123 original, HFN-230,(2) HFN-200 (Hare), HFN-223 (Shah - 2), HFN-258 (RMhatre, Benedek), Drug File